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AMERICAN FARM BUREAU FEDERATION®
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November 23, 2004

Dr. C. W. Jameson
National Toxicology Program Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
PO Box 12233
Research Triangle Park, NC 27709
jameson@niehs.nih.gov

Subject: Department of Health and Human Services. Public Health Service. National Toxicology Program; Call for Additional Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition. Federal Register Notice Vol. 69, No. 205/Monday October 25, 2004; 62276-62279.

Dear Dr. Jameson:

American Farm Bureau Federation (AFBF) submits these comments on the proposed nomination of atrazine listing consideration in the National Toxicology Program's (NTP) Report on Carcinogens (RoC). Farm Bureau is concerned that the NIEHS nominator may not be aware of the recent carcinogenic evaluation of atrazine conducted by EPA, culminating a 10-year review of the herbicide.

AFBF is the nation's largest general farm organization representing farm and ranch families producing food and fiber for the world. Farm Bureau members produce all crops and commodities at many scales of operation.

Atrazine is a critically important product for production of corn and sorghum in the United States and therefore its availability affects producers that produce the safest food supply in the world. Regulatory decisions on products used in crop production must be based on sound science using reliable information and actual data. Implementation must not disrupt agricultural production or undermine U.S. agriculture's competitiveness in international markets. Since EPA has conducted a comprehensive science-based review of atrazine and found that it is not a likely human carcinogen, this apparent abuse of procedure in the case of atrazine is of great concern to the agricultural community.

First, the recommendation for nomination rests only on a selected part of the WHO's International Agency for Research on Cancer's (IARC) decision on atrazine. The National Institute of Environmental Health Sciences (NIEHS) nominator indicates that atrazine should be reviewed on the basis of "IARC finding of sufficient evidence of carcinogenicity in animals". However the most important finding from IARC is left out. That is: "The IARC concluded that while there was sufficient evidence for carcinogenicity in the SD rat, after considering the atrazine mode of action research, the IARC concluded that there was strong evidence that the

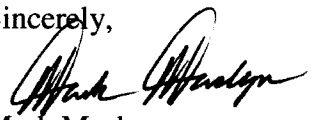
mechanism responsible for mammary tumor formation in the Sprague-Dawley rat is not relevant to humans. The IARC review concludes: "Therefore, there is strong evidence that the mechanism by which atrazine increases the incidence of mammary tumors in Sprague-Dawley rats is not relevant to humans and categorizes atrazine as "not classifiable as to carcinogenicity to humans (Group 3)" (emphasis added).

Second, the EPA has just completed an extensive review of atrazine's carcinogenic potential using both internal and external peer reviews and has concluded that atrazine is "Not likely to be carcinogenic to humans." This is consistent with the IARC review as well as reviews from several other countries. EPA is also aware of the ongoing Agricultural Health Study and has committed to review additional information on atrazine when the study is completed.

Therefore re-review of atrazine by NTP at this time is a waste of taxpayer dollars and is completely unnecessary. Farm Bureau questions the intent of the proposed nomination review in that it may be used to disparage the product by those with an agenda to circumvent the use of sound science in the regulatory process. We also note that in the June, 2004 meeting of the NTP Board of Scientific Counselor's a stated reason for nominating atrazine for review was that "the controversy governing its potential toxicity is not yet settled." Farm Bureau would like to point out that "controversy" is not part of the NTP criteria for listing.

Farm Bureau supports EPA's recommendation that atrazine be removed from the list of additional agents for possible listing in the next edition of the RoC (see attached EPA letter) as duplicative and perhaps undermining to EPA as a federal agency. We believe there is no value in NTP's nomination for listing consideration of atrazine since EPA and IARC have determined there is no basis for concluding that atrazine is/may be carcinogenic to humans, and we request that the nomination be removed from further consideration.

Sincerely,



Mark Maslyn
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Dr. C. W. Jameson
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Report on Carcinogens
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July 19, 2004

Dear Dr. Jameson:

On behalf of the U. S. Environmental Protection Agency (EPA), I am submitting comments on the announcement that the National Toxicology Program (NTP) intends to review the pesticide active ingredient, atrazine, among other agents, for possible listing in the next edition of the Report on Carcinogens (RoC), scheduled for publication in 2006 (69 Federal Register 28940, May 19, 2004). For the reasons described below, EPA recommends that atrazine be removed from the list of additional agents for possible listing in the next edition of the RoC.

As described below, the EPA has devoted considerable resources to the consideration of the potential for atrazine to elicit a carcinogenic response in humans, both within the Agency and through independent, external peer review. We believe that these efforts have produced a scientific consensus on the interpretation of the available scientific information on this topic. Both EPA's review, and a separate review by the International Agency for Research on Cancer (IARC) have concluded that there is not adequate evidence to conclude atrazine is a known human carcinogen or even that it may reasonably be anticipated to be a human carcinogen. While EPA's current opinion is that atrazine does not appear to be a human carcinogen, we are aware that ongoing epidemiological research should produce new data in the coming years that will shed additional light on the potential carcinogenicity of atrazine. When such data become available, EPA has committed to examine them and, if necessary, to revise its conclusions on atrazine and carcinogenicity.

EPA recommends that atrazine be removed from the list of additional agents for possible listing in the next edition of the RoC for several reasons. First, we do not believe that the threshold for undertaking this review has been met; both EPA's and IARC's review did not find evidence of human carcinogenicity. Second, the effort proposed by NTP would be duplicative of work already performed by EPA, as well as work EPA has

committed to perform in the future. Finally, in light of the expected new studies, starting NTP's review at this time could potentially be premature.

Background

EPA regulates pesticides under two statutes. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is responsible for issuing a license, called a registration, to every pesticide product before it may lawfully be sold or distributed. In addition, if use of the pesticide results in residues in food, EPA also establishes maximum allowed limits, "tolerances," for such residues under the Federal Food, Drug, & Cosmetic Act (FFDCA). Under FIFRA, EPA is also responsible for reexamining past decisions to register a pesticide through a program called "reregistration," and, under FFDCA, for reevaluating previously established tolerances through a program referred to as "tolerance reassessment." As part of EPA's reregistration and tolerance reassessment programs, the Agency prepares documents for individual pesticide active ingredients containing a description of the substance's regulatory history, the most current assessment of its human health and environmental risks, and EPA's conclusions regarding its regulatory status under applicable federal laws. These documents, called Reregistration Eligibility Decision (RED) documents, are developed through a transparent, public, participatory process that culminates in the issuance of the RED. In cases when a compound shares a common mechanism of toxicity with other pesticide active ingredients, EPA may issue an interim RED (IRED) for the compound and complete the RED once the Agency has evaluated the cumulative effects of exposure to the group of compounds sharing the common mechanism of toxicity.

EPA issued an IRED for atrazine in January 2003. EPA updated the IRED in October 2003 primarily to address certain issues relating to the ecological risks of atrazine and to discuss the results of its external peer review of data on atrazine and prostate cancer. See http://www.epa.gov/oppsrrd1/reregistration/atrazine/ As described more fully in the IRED, atrazine is a herbicide used to control broadleaf and grassy weeds with major uses on corn, sugarcane, and sorghum, and on a variety of non-agricultural sites, such as lawns and golf courses. Atrazine was first registered as a pesticide in 1958, and the government has established tolerances for the residues of atrazine in a number of raw agricultural commodities. Atrazine is one of the most widely used agricultural pesticides in the United States; approximately 76.5 million pounds are applied domestically each year.

Atrazine Cancer Risk Assessment: History

The IRED summarizes EPA's lengthy consideration of the potential carcinogenicity of atrazine. In 1987, EPA classified atrazine as a possible human carcinogen based on mammary gland tumors in female Sprague Dawley rats. In 1988, the EPA requested its FIFRA Scientific Advisory Panel (SAP) – a federal advisory committee

that provides independent, external expert peer review on scientific issues involving pesticides – to comment on the cancer assessment for atrazine. The SAP recommended that studies be conducted on a potential hormonal mode of action. Since 1988, numerous research studies have been conducted on atrazine's cancer mode of action. Because of the scope and amount of data on atrazine, EPA scientists worked for several years analyzing the studies submitted by the industry, the research data generated by EPA's Office of Research & Development, as well as studies found in the published literature. During this analysis, there were frequent consultations with EPA experts and outside experts.

In June 2000, EPA prepared a document for review by the SAP that contained a detailed evaluation of the mechanistic, animal toxicology, and epidemiology studies pertaining to atrazine's potential carcinogenicity. Refer to documents posted at: http://www.epa.gov/oscpmont/sap/2000/index.htm#060600 . The June 2000 SAP members included well-known experts from the fields of cancer mechanisms and toxicology, epidemiology, experimental and clinical endocrinology, and statistics. The SAP concluded that "it is unlikely that the mechanism by which atrazine induces mammary tumors in female SD rats could be operational in humans" and unanimously disagreed with EPA's proposal to classify atrazine as a likely human carcinogen (this classification would be equivalent to the NTP's RoC category of reasonably anticipated to be a human carcinogen). Although a few epidemiologic studies suggested a possible association between atrazine (or triazine) exposure and certain cancers, the SAP concluded that the lack of multiple studies, internal inconsistencies, and confounding factors in these studies did not indicate a strong causal relationship.

After carefully considering the SAP recommendations, EPA agreed with the SAP and revised its cancer classification for atrazine to "Not likely to be carcinogenic to humans". This cancer classification is consistent with a comprehensive international review conducted by the World Health Organization's International Agency for Research on Cancer (IARC) in 1999. Although IARC stated "[t]here is sufficient evidence in experimental animals for the carcinogenicity of atrazine", based on their evaluation of available mechanistic studies, they concluded that ". . . there is strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumors in Sprague-Dawley rats is not relevant to humans." They also concluded that "[t]here is inadequate evidence in humans for the carcinogenicity of atrazine". See http://www-cie.iarc.fr/htdocs/monographs/vol73/73-03.html

EPA returned to its FIFRA SAP in July 2003 to further consider the epidemiology data on atrazine and specifically to address the issue of prostate cancer. See: http://www.epa.gov/oscpmont/sap/2003/index.htm#071703 . In the paper prepared for the SAP, EPA reviewed several epidemiological studies on atrazine and prostate cancer, including the negative results of the Agricultural Health Study (AHS), a large epidemiology study conducted with farmers who used atrazine and other pesticides, and

the positive results of a study of workers in an atrazine manufacturing facility. EPA also noted that:

> the National Cancer Institute has a number of other analyses in press or planned which are relevant to atrazine. Among these is a re-analysis of earlier studies involving pesticides and non-Hodgkin's lymphoma using hierarchical techniques to adjust for the effects of multiple exposures. This report is expected to be published online in the next 2-3 months. Further, enough additional prostate cancer cases have been added in the Agricultural Health Study since the recent publication that the analysis can be redone with approximately double the number of cases. Re-analysis is planned later this year and may be ready for publication by next year [2004]. An analysis of all the non-Hodgkin's lymphoma cases reported in the Agricultural Health Study is planned to start next year [2004]. And a special analysis of all cancers related to atrazine exposure in the same Agricultural Health Study cohort is also planned for this year with publication expected next year [2004]. In addition, Syngenta is conducting a nested case-control study of workers at the St. Gabriel plant using more detailed job histories to evaluate exposure indices. This study should be available later this year [2003].

EPA stated that, given the importance of incorporating these results into an evaluation of atrazine for prostate cancer and other cancer outcomes, the Agency planned future analyses and that, absent compelling information in the interim, EPA would wait until all of these analyses were in before addressing the broader question of atrazine exposure and cancer.

The July 2003 SAP found the epidemiological information on prostate cancer and atrazine inconclusive. With respect to the study of workers in an atrazine manufacturing facility, the SAP cited factors that would account for an increase in the observed incidence of prostate cancer, but also noted that these factors did not "clearly indicate" they explained all of the increase. The SAP also pointed out several limitations on the AHS. Accordingly, the SAP recommended additional analysis related to prostate cancer and that EPA conduct a broader review of the epidemiology of other cancers and atrazine and other triazines.

EPA studied the SAP report and agreed with these conclusions, which are reflected in the revised atrazine IRED. Since then, additional analysis has been provided of the St. Gabriel workers and prostate cancer, and the retrospective study on non-Hodgkin's lymphoma has been published. Neither study changes the picture meaningfully with respect to atrazine and human carcinogenicity. EPA has not received any other epidemiological data on the carcinogenicity of atrazine, and has learned that some of the studies expected in 2004 will not publish this year. We do not have definite dates for when these additional results would become available.

In sum, EPA's opinion is that there would be no merit in NTP separately considering the cancer classification of atrazine, both because of the extensive review EPA has already performed and the Agency's plans to examine the forthcoming results from ongoing research, especially when neither the EPA nor IARC reviews have concluded that there is a reasonable basis for expecting exposure to atrazine will elicit a carcinogenic response in humans.

Sincerely,

Susan B. Hazen
Principal Deputy Assistant Administrator